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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/609,143	06/27/2003	Lisa C. McConlogue	015270-012100US	6715

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EXAMINER	
CROUCH, DEBORAH	
ART UNIT	**PAPER NUMBER**
1632	

DATE MAILED: 10/11/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/609,143	MCCONLOGUE ET AL.	
	Examiner	Art Unit	
	Deborah Crouch, Ph.D.	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *27 June 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-9* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-9* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *27 June 2003* is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *6/27/03*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

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The preliminary amendment filed June 27, 2003 has been entered. Pending claims are 1-9 are pending.

Applicant should note that this application claims priority to US patent application 08/143,697, filed October 27, 1993. However, '697 is a CIP of two earlier filed applications. However, applicant is not entitled to any priority from the CIP applications as there is no disclosure therein of the presently claimed invention.

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1-9 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-10 of U.S. Patent No. 6,586,656 ('656). Although the conflicting claims are not identical, they are not patentably distinct from each other because the claims are of overlapping and obvious scope.

Present claims 1-9 are to transgenic nonhuman animals or stem cells comprising a diploid genome comprising a transgene encoding a heterologous APP-Swedish where amino acids corresponding to positions 595 and 596 in human APP695 are asparagines and leucine

and a transgene encoding a human APP-Swedish operably lined to transcriptional control sequences.

Present claims 1-9 are obvious over claims 1-10 in '656 as the method claimed therein makes the presently claimed nonhuman animal, and the presently claimed transgene is specifically used in the method claimed in '656. The nonhuman mammals of present claims 1-5 are defined by the specification as for Alzheimer's treatment assays.

Thus at the time of the present invention, the ordinary artisan would have found present claims 1-9 obvious given claims 1-10 of '656.

Claims 1-9 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-10 of U.S. Patent No. 6,245,964 B1 ('964). Although the conflicting claims are not identical, they are not patentably distinct from each other because the claims are of overlapping and obvious scope.

Present claims 1-9 are to transgenic nonhuman animals or stem cells comprising a diploid genome comprising a transgene encoding a heterologous APP-Swedish where amino acids corresponding to positions 595 and 596 in human APP695 are asparagines and leucine and a transgene encoding a human APP-Swedish operably lined to transcriptional control sequences.

Present claims 1-9 are to a transgenic nonhuman animal and a transgene that are encompass claims 1-8 of '964. Further the to methods of producing transgenic rodents, claims 9 and 10 of '964 are used to produce the presently claims nonhuman mammals using the presently claimed transgene. Further, the presently claimed nonhuman animals of claims 1-5 can be used in the drug screening methods, claims 11-15 of '964.

At the time of the instant invention, it would have been obvious to the ordinary artisan to implement the claims methods of producing rodents and methods of using the produced rodent given the claims of '964.

Claims 1-9 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-4 of U.S. Patent No. 5,850,003. Although the conflicting claims are not identical, they are not patentably distinct from each other because the presently claimed transgenic nonhuman animals are generic to those of claims 1-4 of '003.

Present claims 1-9 are to transgenic nonhuman animals or stem cells comprising a diploid genome comprising a transgene encoding a heterologous APP-Swedish where amino acids corresponding to positions 595 and 596 in human APP695 are asparagines and leucine and a transgene encoding a human APP-Swedish operably lined to transcriptional control sequences.

The present claims 1-6 are generic to those of '003, in that each limitation of the claims in '003 can be found within the present claims. The transgene of present claims 7-9 is the transgene found in the rodents of claims 1-4 in '003.

Thus at the time of the instant invention, it would have been obvious to the ordinary artisan to arrive at the presently claimed nonhuman rodents and transgenic given the claims in '003.

Claims 1-9 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-4 of U.S. Patent No. 5,612,486. Although the conflicting claims are not identical, they are not patentably distinct from each other because the presently claimed transgenic nonhuman animals are generic to those of claims 1-4 of '486.

Present claims 1-9 are to transgenic nonhuman animals or stem cells comprising a diploid genome comprising a transgene encoding a heterologous APP-Swedish where amino acids corresponding to positions 595 and 596 in human APP695 are asparagines and leucine

and a transgene encoding a human APP-Swedish operably lined to transcriptional control sequences.

The present claims 1-6 are generic to those of '486, in that each limitation of the claims in '486 can be found within the present claims. The transgene of present claims 7-9 is the transgene found in the rodents of claims 1-4 in '486.

Thus at the time of the instant invention, it would have been obvious to the ordinary artisan to arrive at the presently claimed nonhuman rodents and transgenic given the claims in '486.

Claims 1-9 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-16 of U.S. Patent No. 5,604,102. Although the conflicting claims are not identical, they are not patentably distinct from each other because the claims are of overlapping scope.

Present claims 1-7 are to transgenic nonhuman animals or stem cells comprising a diploid genome comprising a transgene encoding a heterologous APP-Swedish where amino acids corresponding to positions 595 and 596 in human APP695 are asparagines and leucine. The present claims are defined as being an Alzheimer's disease model.

The presently claimed transgenic nonhuman animals can be used in the methods of claims 1-16 of '102 as the methods require rodents comprising an APP-Swedish mutation.

Thus at the time of the instant invention, it would have been obvious to the ordinary artisan to use the presently claimed nonhuman mammals in the assay systems of claims 1-16 of '102.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 3 and 9 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Claims 3 and 9 require specific plasmids, pNSEAPPswΔ3' or pNSEAPPsw. However, the specification does not provide a reproducible source, readily available to the public for these plasmids. In order for claims 3 and 9 to comply with the requirements for enablement under 35 U.S.C. § 112, first paragraph, plasmids pNSEAPPswΔ3' or pNSEAPPsw must be deposited. If the deposit is made under the terms of the Budapest Treaty, then an affidavit or declaration by applicants, or a statement by an attorney of record over his or her signature and registration number, stating that the plasmids have been deposited under the Budapest Treaty and that the plasmids will be irrevocably and without restriction or condition released to the public upon the issuance of a patent, would satisfy the deposit requirement made herein. 37 CFR 1.808

If the deposit has not been made under the Budapest Treaty, then in order to certify that the deposit meets the criteria set forth in 37 CFR 1.808, applicants may provide assurance of compliance by an affidavit or declaration, or by a statement by an attorney of record over his or her signature and registration number, showing that

(a) during the pendency of this application, access to the invention will be afforded to the Commissioner upon request;
(b) all restrictions upon availability to the public will be irrevocably removed upon granting of the patent;
(c) the deposit will be maintained in a public depository for a period of 30 years or 5 years after the last request or for the effective life of the patent, whichever is longer;
(d) a viability statement in accordance with the provisions of 37 CFR 1,807; and
(e) the deposit will be replaced if it should ever become inviable.

As required under 37 CFR 1.809(d), the specification shall contain: (1) the accession number for the deposit; (2) the date of deposit; (3) a description of the deposited biological

material sufficient to identify it and to permit its examination; and (4) the name and address of the depository. While Figure 1a shows map of the deletion clone, guidance is not given how to make the specific plasmids pNSEAPPswΔ3' or pNSEAPPsw.

Claim 1 is rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for mouse embryonic stem cells comprising a diploid genome comprising a transgenic encoding a heterologous APP poly peptide comprising the Swedish mutation wherein the amino acid residues at positions corresponding to positions 595 and 596 of human APP695, does not reasonably provide enablement for stem cells. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Claim 1 is to a stem cell comprising a diploid genome comprising a heterologous APP polypeptide comprising the Swedish mutation wherein amino acids 595 and 596 of APP695 are asparagines and leucine. The lacks an enabled use.

The specification discloses embryonic stem cells for the production of gene targeted animals, where the Swedish mutation is specifically inserted into the APP genome (specification, page 7, lines 12-20). However, at the time of filing the prior art and post-filing art are replete with references which indicate that ES cell technology is limited to the mouse system, at present, and that only "putative" ES cells exist for other species. See Moreadith et al. (J. Mol. Med., 1997), page 214, Summary. In addition, Seamark (Reproductive Fertility and Development, 1994) discloses that totipotency of ES cell technology in many livestock species has not been demonstrated (page 6, Abstract). Mullins et al. (Journal of Clinical Investigation, 1996) disclose that "although to date chimeric animals have been generated from several species including the pig, in no species other than the mouse has germline transmission of an ES cell been successfully demonstrated" (page S38, col. 1, first. parag.). There is only a disclosed use for ES cells in the production of transgenic animals.

Claims 1-6 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for transgenic rodents comprising a diploid genome comprising a heterologous APP polypeptide comprising the Swedish mutation wherein amino acids 595 and 596 of APP695 are asparagine and leucine, and where expression of the transgene results in the production of human APP having a Swedish mutation and wherein the human APP is processed to ATF-beta AFP in detectable amounts in brain homogenates of the mouse, does not reasonably provide enablement for transgenic nonhuman animals. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Claims 1-6 are to a transgenic nonhuman animal comprising a diploid genome comprising a heterologous APP polypeptide comprising the Swedish mutation wherein amino acids 595 and 596 of APP695 are asparagines and leucine. However, at the time of filing, the skilled artisan would only have regarded rodents

The specification indicates that the mice are to be used as assay models, where the production of the ATF-beta AFP cleavage product is assayed in response to test compounds (page 21, lines 4-24). Thus, for the claimed animals to have an enabled use, the claims must have such an assay endpoint. Animals lacking such a proteolytic fragment have no use in view of the disclosure.

At the time of filing, the skilled artisan would have only regarded the scope of rodent enabled because the art taught that the development of an Alzheimer's disease phenotype in animal models was unpredictable. When amyloid cores are injected into the brains of monkeys, the monkeys do not develop neurotoxicity (Podlisny et al (1992) Neurobiol. Aging 13, page 562, col. 2, parag. 3). In addition, the art also taught that the production of transgenic mice expressing an APP transgene had been problematic, and that the reason

was mice as a species may be resistant to the formation of Alzheimer's related pathologies and that sufficient expression of the APP transgene may be difficult to achieve (Lannfelt et al (1993) Behav. Brain Res. 57. page 210, col. 1, parag. 5; and col. 2, parag. 4, lines 8-16). In addition, applicant has shown that the transgenic mice show a Also, at the time filing, the art taught that transgenic rats containing an APP transgene failed to demonstrate any Alzheimer's related pathology at six months of age (Felsenstein et al (1995) Alzheimer's and Parkinson's Diseases, I. Hanin, ed., Plenum Press, New York, page 406, page 1). Thus, the development of an Alzheimer's disease model was unpredictable at the time of filing.

Thus, claims 1-6 lack enablement because the skilled artisan would have needed to engage in an undue amount of experimentation without a predictable degree of successes to implement the claimed invention for all reasons stated above.

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 1, 2, 4, 5 and 7 are rejected under 35 U.S.C. 102(b) as anticipated by U.S. Patent 5,455,169 (Mullan) issued Oct. 3, 1995.

Mullan teaches a transgene comprising a DNA sequence encoding human amyloid APP 770 comprising the Swedish mutation, K670N and M671L operably linked to a promoter (col. 7, lines 11-42; col. 11, lines 44-50). Mullan further teaches the use of this transgene in the production of nonhuman animals, especially mice or rats (col. 11, lines 50-56 and col. 14, lines 5-17). Mullan human amyloid is subject to processing the brain where three splice

variants are formed: APP695, APP751 and APP770 (col. 1, lines 55-62). Thus, the specific APP variant claimed is APP695 comprising the above Swedish mutations (col. 12, line 66 to col. 13, line 3). Therefore, Mullan clearly anticipates the invention as claimed.

It is noted that the novel feature of applicant's invention is the finding of APP cleavage products in brain homogenate. Applicant should consider amending the claims to reflect this as in previously allowed claims.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1, 6, 7 and 8 are rejected under 35 U.S.C. 103(a) as being unpatentable over Patent 5,455,169 (Mullan) issued Oct. 3, 1995 in view of Quon et al. (1991) Nature 352, pp. 239-241.

Mullan teaches a transgene comprising a DNA sequence encoding human amyloid APP 770 comprising the Swedish mutation, K670N and M671L operably linked to a promoter (col. 7, lines 11-42; col. 11, lines 44-50). Mullan further teaches the use of this transgene in the production of nonhuman animals, especially mice or rats (col. 11, lines 50-56 and col. 14, lines 5-17). Mullan human amyloid is subject to processing the brain where three splice variants are formed: APP695, APP751 and APP770 (col. 1, lines 55-62). Thus, the specific APP variant claimed is APP695 comprising the above Swedish mutations (col. 12, line 66 to col. 13, line 3). Quon teaches a transgene comprising a DNA sequence encoding APP751 operably linked to a rat neuronal specific enolase promoter (page 239, col. 2, parag. 1, lines 1-7). Resulting mice exhibited amyloid deposits in their brains. (page 240, figure 2). Further, Quon teaches the transgenic mice as models for Alzheimer's disease as the mice

exhibit brain structures similar to those seen Alzheimer's disease patients (page 241, parag. 2, lines 10-14). Mullan offers motivation in stating the animals can be used as Alzheimer's disease models (col. 10, line 66 to col. 11, line 8).

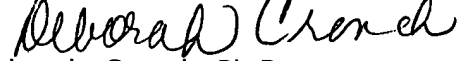
Thus at the time of the instant invention, it would have been obvious to the ordinary artisan to make transgenic mice and a transgene comprising APP695-SWE as taught by Mullan operably linked to a rat neuronal specific enolase promoter as taught Quon to produce mice models for Alzheimer's disease. The cited prior art provides the requisite teaching, suggestion and motivation.

It is noted that the novel feature of applicant's invention is the finding of APP cleavage products in brain homogenate. Applicant should consider amending the claims to reflect this as in previously allowed claims.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Deborah Crouch, Ph.D. whose telephone number is 571-272-0727. The examiner can normally be reached on M-Fri, 7:30 AM to 4:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla, Ph.D. can be reached on 571-272-0735. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).



Deborah Crouch, Ph.D.
Primary Examiner
Art Unit 1632

October 3, 2005